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CRISPR-Cas9 Delivery via Nanocarriers for Precision Oncology: Progress and Pitfalls

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ABSTRACT

CRISPR-Cas9 genome editing has revolutionized cancer research and therapy by offering unprecedented precision in targeting oncogenes, tumor suppressors, and key regulatory pathways. However, the therapeutic potential of CRISPR in oncology remains hindered by challenges related to the efficient and safe delivery of the CRISPR-Cas9 components to tumor cells. Nanocarrier-based delivery systems have emerged as promising vehicles to overcome these hurdles, enhancing cellular uptake, tissue-specific targeting, endosomal escape, and minimizing immunogenicity. This review outlines recent advances in nanocarrier technologies, including lipid nanoparticles, polymeric carriers, gold nanoparticles, exosomes, and DNA nanostructures, engineered for the delivery of CRISPR-Cas9 to solid tumors and hematological malignancies. We highlight their applications in editing cancer-relevant genes, modulating the tumor microenvironment, and overcoming drug resistance. Despite the progress, several pitfalls remain, including off-target effects, immunogenic responses, limited tumor penetration, and scalability concerns. We discuss the translational challenges and propose strategies to optimize the efficacy and safety of CRISPR-Cas9 nanodelivery platforms. This review concludes by exploring future directions in the development of personalized, tumor-targeted CRISPR-based gene therapies for precision oncology.

Keywords: CRISPR-Cas9, Nanocarriers, Precision Oncology, Gene Editing, Targeted Cancer Therapy

INTRODUCTION

The landscape of oncology has witnessed a significant transformation in recent years due to the advent of precision medicine**,** a novel approach that tailors therapeutic interventions to the individual genetic, molecular, and environmental makeup of each patient[1–3]. This shift towards a more personalized treatment paradigm has been fueled by major advances in genomic technologies, one of the most revolutionary being the CRISPR-Cas9 genome editing system**.** Derived from an adaptive immune defense mechanism found in bacteria and archaea, CRISPR-Cas9 enables precise modifications in the DNA sequence, offering unprecedented opportunities for the treatment and understanding of cancer at the genetic level[4–6].

CRISPR-Cas9 comprises two essential components: a guide RNA (gRNA) that identifies and binds to a specific DNA sequence, and the Cas9 endonuclease that introduces a double-strand break at the target site[7, 8]. This break can subsequently be repaired by cellular pathways such as non-homologous end joining (NHEJ) or homology-directed repair (HDR), resulting in gene disruption or correction, respectively. In cancer research, this capability has opened up multiple avenues including the inactivation of oncogenes, restoration of tumor suppressor genes, induction of synthetic lethality, identification of drug-resistance mechanisms, and the engineering of immune cells for more effective cancer immunotherapy[9].

Despite its tremendous therapeutic potential, the translation of CRISPR-Cas9 technology from bench to bedside is still in its infancy. One of the primary barriers is the challenge of efficient, targeted, and safe delivery of CRISPR components to tumor cells in vivo[10]. While viral vectors such as lentiviruses and adeno-associated viruses have traditionally been used due to their high transduction efficiency, they suffer from significant limitations including immunogenicity, potential for insertional mutagenesis**,** limited packaging capacity, and manufacturing complexities[10].

In response to these limitations, researchers have turned to nanotechnology-based delivery systems as a promising non-viral alternative[11–14]. Nanocarriers including lipid nanoparticles, polymeric nanoparticles, dendrimers, inorganic nanomaterials, and exosomes can be tailored to overcome physiological barriers such as degradation in the bloodstream, immune clearance, off-target distribution, and cellular uptake limitations[15–

17]. These delivery systems are capable of encapsulating various CRISPR components including Cas9 protein complexed with gRNA (ribonucleoprotein, or RNP), plasmids encoding CRISPR elements, or Cas9 mRNA. The surface of nanocarriers can be modified with targeting ligands (such as antibodies, aptamers, or peptides) to increase specificity toward tumor tissues or cancer stem cells[18, 19].
Moreover, nanocarriers can be designed to be stimuli-responsive, releasing their cargo only under certain conditions such as acidic pH, high glutathione levels, or the presence of tumor-specific enzymes, thereby enhancing spatiotemporal control over gene editing events[5, 20–22]. This can significantly reduce the off-target effects and systemic toxicity associated with traditional gene editing strategies. Importantly, many nanocarriers exhibit biodegradability and biocompatibility, which are essential for their clinical translation.

In this review, we present a comprehensive analysis of the current state of CRISPR-Cas9 delivery via nanocarriers, with a specific focus on applications in precision oncology. We begin by exploring the mechanism and applications of CRISPR-Cas9 in cancer biology, followed by an in-depth discussion of the different types of nanocarriers and their physicochemical properties, delivery mechanisms, and therapeutic potential. We highlight findings from recent preclinical models and early-phase clinical trials, assessing both the benefits and limitations of various delivery strategies.
Finally, we discuss future perspectives and the path forward in optimizing nanocarrier design, minimizing toxicity, and improving targeting efficiency. The integration of CRISPR-Cas9 with nanotechnology has the potential to revolutionize cancer treatment by enabling precise, customizable interventions. However, careful consideration of delivery mechanisms, off-target effects, immunogenicity, and long-term safety is imperative for the successful clinical application of this powerful genome editing technology.

2. Overview of CRISPR-Cas9 in Cancer Therapy

The CRISPR-Cas9 gene-editing system represents a transformative platform in the field of oncology, allowing for precise, programmable modifications to the genome. At its core, CRISPR-Cas9 employs a single-guide RNA (sgRNA) to direct the Cas9 endonuclease to a target DNA sequence[23–25]. Once the double-strand break (DSB) is introduced, the cell's endogenous repair machinery is activated. The non-homologous end joining (NHEJ) pathway often introduces small insertions or deletions, leading to gene disruption, while homology-directed repair (HDR) can be used for precise gene correction when a homologous repair template is provided[25–27].
In cancer therapy, CRISPR-Cas9 offers several promising applications. One major use is the inactivation of oncogenes such as KRAS, MYC, and EGFR, which are frequently mutated or overexpressed in various cancers, including colorectal, pancreatic, lung, and breast cancer. By targeting these driver mutations, CRISPR can halt tumor proliferation, induce apoptosis, or resensitize cancer cells to chemotherapy[27]. Another application is the restoration of tumor suppressor genes like TP53 and PTEN, which are commonly inactivated in tumors. Reinstating their function can restore normal cell cycle control and apoptotic responses[28].
CRISPR-Cas9 also plays a critical role in cancer immunotherapy. It has been used to reprogram T cells to enhance their anti-tumor activity. For instance, T cells engineered to knock out PD-1 or CTLA-4 using CRISPR demonstrate enhanced persistence and cytotoxicity against tumors, especially when used in combination with immune checkpoint inhibitors[29]. CRISPR has also been employed to generate chimeric antigen receptor (CAR) T cells with improved specificity and reduced exhaustion, offering a novel approach for hematologic malignancies and, increasingly, for solid tumors[29].
Additionally, CRISPR has facilitated functional genomics screens to identify novel cancer vulnerabilities and synthetic lethal interactions[30, 31]. These large-scale screens have uncovered genes involved in DNA repair, apoptosis, metabolism, and immune evasion that can be targeted for therapeutic gain. CRISPR-based editing has also been used to model cancer progression in animal models by introducing combinations of driver mutations, thereby providing valuable insights into tumor biology and aiding drug discovery[30]. Despite these advances, several challenges remain, the most significant of which is the efficient and specific delivery of CRISPR components to tumor cells in vivo. Delivery must overcome numerous physiological barriers, including nuclease degradation, immune detection, cellular uptake, and nuclear localization. The form in which CRISPR components are delivered, be it DNA, mRNA, or ribonucleoprotein (RNP), also influences the editing efficiency and duration of action[32].
This is where nanocarrier systems hold considerable promise. Nanocarriers such as lipid nanoparticles (LNPs), polymeric nanoparticles, dendrimers, gold nanoparticles, and extracellular vesicles can encapsulate and protect CRISPR components, facilitate cellular uptake, and enhance tumor-specific delivery through passive or active targeting strategies[33]. For instance, LNPs have been successfully used to deliver Cas9 mRNA and gRNA in models of liver and lung cancer, leading to significant gene disruption with minimal off-target effects[33]. Moreover, nanocarriers can be engineered to respond to tumor-specific stimuli, such as acidic pH, enzymes, or redox gradients, ensuring site-specific release of CRISPR cargo. This level of control is crucial in reducing systemic side effects and increasing editing precision. Importantly, nanocarriers can be modified with tumor-targeting ligands such as antibodies, peptides, or aptamers to further enhance delivery specificity[34].

CRISPR-Cas9 offers a powerful and flexible tool for cancer therapy, with applications spanning gene inactivation, gene correction, immune cell engineering, and functional genomics. However, its full clinical potential can only be realized with the development of effective and safe delivery systems—an area where nanotechnology plays a pivotal role. The convergence of genome editing and nanomedicine thus holds the key to the next generation of precision oncology therapies.

3. Nanocarier Platforms for CRISPR-Cas9 Delivery

3.1 Lipid Nanoparticles (LNPs): Lipid nanoparticles (LNPs) have emerged as one of the most promising non-viral delivery platforms for CRISPR-Cas9 gene-editing systems, particularly due to their successful application in mRNA vaccine technology[35–37]. Their structure typically comprises ionizable lipids, phospholipids, cholesterol, and polyethylene glycol-lipids, which together facilitate efficient encapsulation and protection of nucleic acids or ribonucleoprotein complexes (RNPs). The ionizable lipids, in particular, become positively charged in acidic environments, such as within endosomes, enabling effective endosomal escape and intracellular release of CRISPR components. This property significantly enhances genome editing efficiency[38–40]. Moreover, LNPs can be modified with targeting ligands to improve tumor-specific delivery. Preclinical studies have demonstrated that LNPs can effectively deliver CRISPR tools targeting oncogenes such as KRAS and PCSK9, leading to promising antitumor responses. Their high biocompatibility, scalability, and ability to deliver both mRNA and protein formats make LNPs highly adaptable and attractive for therapeutic genome editing in oncology.

3.2 Polymeric Nanoparticles: Polymeric nanoparticles are widely explored as CRISPR-Cas9 delivery vehicles owing to their customizable physicochemical properties, which include size, surface charge, biodegradability, and release kinetics[41–43]. Commonly used polymers such as polyethyleneimine (PEI), poly(lactic-co-glycolic acid) (PLGA), and chitosan have demonstrated the ability to encapsulate and protect nucleic acids, as well as Cas9 mRNA or RNPs. Their surface can be easily functionalized with targeting ligands or PEG to enhance circulation time and tumor specificity. Importantly, polymeric carriers offer tunable degradation rates, which can be tailored to release CRISPR payloads at desired intracellular locations[43–45]. However, a major limitation lies in their sometimes high cytotoxicity, especially with cationic polymers like PEI, and their inefficiency in escaping endosomes. These drawbacks have spurred efforts in polymer modification, such as the addition of pH-responsive or fusogenic domains. Despite these challenges, polymeric nanoparticles remain a flexible and evolving platform for CRISPR-based gene editing, particularly in targeted cancer therapy applications[46].

3.3 Gold Nanoparticles (AuNPs): Gold nanoparticles (AuNPs) offer a unique platform for CRISPR-Cas9 delivery due to their high surface-area-to-volume ratio, ease of functionalization, and inert chemical nature[13, 47, 48]. Their ability to form stable bonds with thiol-modified DNA or RNA makes them excellent scaffolds for attaching CRISPR components such as guide RNAs and Cas9 protein. One innovative application of AuNPs is in light-responsive delivery systems, where external stimuli such as near-infrared (NIR) light can trigger the release of CRISPR payloads in a spatially controlled manner—particularly advantageous in localized cancer therapy. Moreover, AuNPs show minimal immunogenicity and are relatively non-toxic at therapeutic doses[49–51]. Their optical properties also allow for imaging and tracking, making them useful in theranostic applications. However, concerns persist regarding their potential long-term accumulation in tissues and the high cost of large-scale production. Nonetheless, AuNPs remain a promising tool for precision oncology, offering targeted, controllable, and efficient delivery of CRISPR-based therapeutics.

3.4 Exosomes and Extracellular Vesicles: Exosomes and other extracellular vesicles (EVs) have gained significant attention as natural delivery systems for CRISPR-Cas9 components due to their intrinsic ability to transfer biomolecules across cell membranes while evading immune recognition[6, 52, 53]. These vesicles are derived from cellular membranes and can be engineered to carry Cas9 mRNA, RNPs, or plasmids, making them suitable for gene-editing applications. Their endogenous origin contributes to high biocompatibility and minimal toxicity. A major breakthrough has been the successful use of engineered exosomes to cross physiological barriers like the blood-brain barrier (BBB), enabling gene editing in hard-to-reach tissues such as the brain[54–56]. For instance, glioma-targeting exosomes have shown efficacy in delivering CRISPR-Cas9 constructs across the BBB in preclinical models. However, challenges remain in the reproducible isolation, loading efficiency, and large-scale manufacturing of exosomes, which limit their immediate clinical translation. Despite these hurdles, exosomes offer a biologically harmonious and non-immunogenic route for CRISPR delivery, particularly in cancer gene therapy[54, 57].

3.5 DNA Nanostructures and Metal-Organic Frameworks (MOFs): DNA nanostructures and metal-organic frameworks (MOFs) are emerging as highly customizable platforms for CRISPR-Cas9 delivery[58]. DNA nanostructures, such as DNA origami, allow precise spatial arrangement of Cas9 components, enabling controlled release and enhanced stability[59]. These structures are biocompatible, programmable, and can be modified with targeting ligands or chemical cues for tumor-specific delivery[59]. On the other hand, MOFs are porous crystalline materials composed of metal ions coordinated to organic ligands, offering exceptionally high loading capacity and protection for CRISPR cargos. MOFs can respond to pH or redox changes in the tumor

microenvironment, triggering selective release of CRISPR agents. While both systems are still in the early stages of development, initial studies suggest their potential in facilitating targeted, efficient, and minimally toxic genome editing[60]. Their modularity and ability to incorporate multiple functionalities make DNA nanostructures and MOFs attractive for future cancer therapies, though issues such as in vivo stability and immune clearance still need to be addressed.

4. Applications in Precision Oncology

The integration of nanocarrier-mediated CRISPR-Cas9 delivery systems into precision oncology has significantly expanded the landscape of targeted cancer therapies. These nanoscale delivery vehicles have enabled precise genome editing directly within tumor cells or immune components, leading to groundbreaking therapeutic applications.

One key application involves the targeting of oncogenes and tumor suppressor genes. For instance, lipid nanoparticles (LNPs) and gold nanoparticles (AuNPs) have been effectively employed to deliver CRISPR-Cas9 constructs targeting the mutant *KRAS* gene, which is notoriously difficult to treat in pancreatic and non-small cell lung cancers[61]. Editing this gene has resulted in suppressed tumor growth, decreased metastasis, and improved survival outcomes in preclinical models[62]. Another vital area is the reversal of drug resistance. Many tumors develop resistance to chemotherapeutic agents through the upregulation of multidrug resistance genes, such as members of the ATP-binding cassette (ABC) transporter family. Nanocarriers have been used to deliver CRISPR-Cas9 components that knock out these resistance genes, thereby restoring tumor sensitivity to standard chemotherapy drugs and enhancing treatment efficacy[62].

Immune modulation represents an equally promising avenue. Using exosomes or LNPs to deliver CRISPR-Cas9 to T cells allows the disruption of immune checkpoints such as *PD-1*, thereby reinvigorating cytotoxic T-cell responses against tumors[63]. Additionally, CRISPR has been used to edit genes encoding immunosuppressive cytokines in the tumor microenvironment, shifting the immune milieu toward an anti-tumor phenotype and potentiating immune checkpoint inhibitors[63, 64].

Lastly, synthetic lethality-based strategies have emerged, wherein CRISPR-mediated knockout of specific genes is combined with targeted drug therapies. A notable example is the targeting of DNA damage response genes in conjunction with PARP inhibitors in BRCA-mutated tumors, yielding synergistic cytotoxic effects and minimizing resistance mechanisms[65]. Collectively, these applications highlight the transformative role of nanocarrier-enabled CRISPR-Cas9 in next-generation precision oncology.

5. Pitfalls and Challenges

5.1 Off-Target Effects and Genomic Instability: A major limitation of CRISPR-Cas9 delivery in precision oncology is the potential for off-target DNA cleavage, which can lead to unintended genetic alterations, genomic instability, or even promote oncogenesis[66]. These unintended effects challenge the safety profile of CRISPR therapeutics. To minimize these risks, researchers are developing high-fidelity Cas9 variants with enhanced specificity, such as eSpCas9 and SpCas9-HF1[66]. Additionally, the use of paired Cas9 nickases, which create single-strand breaks requiring dual binding, further improves target precision. Delivering Cas9 as short-lived mRNA or ribonucleoproteins (RNPs) also limits its activity window, reducing the likelihood of off-target events.

5.2 Inefficient Tumor Targeting: Tumor heterogeneity, dense extracellular matrix (ECM), and poor vascularization limit efficient nanoparticle (NP) delivery. While passive targeting via the enhanced permeability and retention (EPR) effect provides some advantage, it is inconsistent across tumor types[67]. To improve precision delivery, active targeting using ligands such as antibodies, peptides, or aptamers against tumor-specific receptors (e.g., EGFR, HER2, or CD44) is increasingly employed. These ligands help guide nanoparticles across biological barriers and enhance accumulation in tumor tissues, improving CRISPR-Cas9 therapeutic outcomes[67].

5.3 Immune Responses and Toxicity: Immune activation against Cas9 protein—particularly from *Streptococcus pyogenes* or *Staphylococcus aureus*—and synthetic nanocarriers is a growing concern[68]. Repeated dosing may trigger adaptive immunity, leading to reduced efficacy or adverse reactions. Strategies to reduce immunogenicity include PEGylation of nanoparticles to camouflage them from immune surveillance, and the engineering of humanized or less immunogenic Cas9 variants. Monitoring immune responses during treatment is also vital for patient safety[68].

5.4 Manufacturing and Scalability: The translation of CRISPR-nanocarrier systems to clinical use is hindered by complex manufacturing processes[69]. Challenges include reproducibility in nanoparticle synthesis, batch-to-batch variability, and stringent regulatory requirements. Ensuring quality control through standardized protocols, good manufacturing practices (GMP), and scalable technologies like microfluidics or self-assembly platforms is essential to facilitate clinical deployment and commercialization[69].

6. Future Perspectives

The future of CRISPR-Cas9 delivery via nanocarriers in oncology is promising but requires further refinement. Innovations in biodegradable nanomaterials, multi-modal imaging-guided delivery, and smart responsive systems that release payloads upon tumor-specific triggers will enhance precision. Integration with artificial intelligence and machine learning may accelerate the design of personalized delivery platforms based on patient-

specific tumor profiles. Furthermore, clinical trials evaluating the safety, efficacy, and biodistribution of CRISPR-nanocarrier systems are essential to bridge the gap between laboratory and clinic.

CONCLUSION

Nanocarrier-mediated delivery of CRISPR-Cas9 represents a transformative approach in precision oncology, offering new strategies to target the genetic underpinnings of cancer. While remarkable progress has been made in designing effective delivery vehicles, several biological, technical, and regulatory challenges must be addressed. Continued interdisciplinary research is vital to unlocking the full therapeutic potential of CRISPR in cancer care, paving the way for next-generation personalized gene therapies.

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